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Atezolizumab (NSCLC; first line) –

Addendum to Commission A21-69[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SAE	serious adverse event

1 Background

On 12 October 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-69 (Atezolizumab – benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter "company") has submitted an indirect comparison for the assessment of atezolizumab versus the appropriate comparator therapy (ACT) pembrolizumab using the common comparator of platinum-based chemotherapy; this indirect comparison was used in the benefit assessment. However, the outcomes of serious adverse events (SAEs), severe adverse events (AEs) (operationalized as Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), and discontinuation due to AEs failed to show sufficient certainty of results to justify an adjusted indirect comparison and were consequently disregarded in the benefit assessment.

After the oral hearing [3], the G-BA commissioned IQWiG with assessing the data submitted in the company's dossier [2]:

- Research question 1 (patients with a tumour proportion score [TPS] ≥ 50%): analysis of the adjusted indirect comparison for the side effect outcomes (SAEs, severe AEs, discontinuation due to AEs).

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The company's dossier presents an adjusted indirect comparison on the basis of the IMpower110 study for the atezolizumab side and the KEYNOTE 024 and KEYNOTE 042 studies on the pembrolizumab side (for a detailed discussion of the studies, see dossier assessment A21-69 [1]).

Incomplete data submitted by the company on the KEYNOTE 042 study

As described in dossier assessment A21-69, the company's dossier presents results for the entire relevant subpopulation (N = 599) of the KEYNOTE 042 study only for the outcome of all-cause mortality. However, additional side effects analyses of the KEYNOTE 042 study, which were not included in the company's dossier, are available from the benefit assessment procedures 2019-04-01-D-447 + 2019-04-01-D-448 [4,5]. These analyses are limited to patients for whom carboplatin represents a suitable treatment option according to a retrospective investigator survey carried out by the company in accordance with the specifications of the Pharmaceuticals Directive (AM-RL) on off-label use (Section K of Annex VI). These analyses were performed separately for patients with squamous epithelial (N = 120) versus non-squamous epithelial histology (N = 176) and hence comprise slightly less than 50% of the relevant subpopulation of the KEYNOTE 042 study. With its comment [6], the company subsequently submitted analyses of the KEYNOTE 042 study, but these included results only for patients with non-squamous epithelial histology from procedure 2019-04-01-D-447 [4].

Side effects results exhibit high risk of bias

The results on the outcomes of SAEs, severe AEs, and discontinuation due to AEs obtained from the adjusted indirect comparison on the basis of the IMpower110 and KEYNOTE 024 studies lack the certainty of results required for performing an adjusted indirect comparison. For the outcomes of SAEs and severe AEs, this is because of a high risk of bias of results due to incomplete observation for potentially informative reasons after treatment discontinuation. The high risk of bias regarding the results on the outcome "discontinuation due to AEs" is due to the lack of blinding in the studies against the backdrop of the subjective recording of the outcome.

Below, the results of the adjusted indirect comparison for the side effects outcomes are presented as per the terms of the commission.

Results

Table 1 shows the results of the adjusted indirect comparison for the side effects outcomes. Kaplan-Meier curves on the side effects outcomes are available in Annex B of dossier assessment A21-69 [1].

Table 1: Results (side effects) – RCT, indirect comparison: atezolizumab vs. pembrolizumab, patients with high PD-L1 expression (multipage table)

Outcome category Outcome Comparison Study	Atezolizumab or pembrolizumab N	Atezolizumab or pembrolizumab Median time to event in months [95% CI] Patients with event n (%)	Platinum-based chemotherapy N	Platinum-based chemotherapy Median time to event in months [95% CI] Patients with event n (%)	Group difference HR [95% CI]; p-value
Side effects					
SAEs					
Atezolizumab vs. platinum-based chemotherapy					
IMpower110 (data cut-off 10 September 2018)	134	ND 39 (29.1)	114	ND 31 (27.2)	0.87 [0.54; 1.41]; 0.579[a]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE 024 (data cut-off 9 May 2016)	154	ND 68 (44.2)	150	ND 66 (44.0)	1.00 [0.71; 1.41]; 0.994[b]
KEYNOTE 042 (data cut-off 26 February 2018)		ND		ND	ND
Indirect comparison using common comparators[c]:					
atezolizumab vs. pembrolizumab					0.87 [0.48; 1.57]; 0.645[d]
Severe AEs[e]					
Atezolizumab vs. platinum-based chemotherapy					
IMpower110 (data cut-off 10 September 2018)	134	ND 43 (32.1)	114	ND 62 (54.4)	0.37 [0.25; 0.56]; < 0.001[a]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE 024 (data cut-off 9 May 2016)	154	ND 82 (53.2)	150	ND 109 (72.7)	0.49 [0.36; 0.66]; < 0.001[b]
KEYNOTE 042 (data cut-off 26 February 2018)		ND		ND	ND
Indirect comparison using common comparators[c]:					
atezolizumab vs. pembrolizumab					0.76 [0.46; 1.25]; 0.282[d]
Discontinuation due to AEs					
Atezolizumab vs. platinum-based chemotherapy					
IMpower110 (data cut-off 10 September 2018)	134	ND 5 (3.7)	114	ND 25 (21.9)	0.12 [0.05; 0.32]; < 0.001[a]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE 024 (data cut-off 9 May 2016)	154	ND 14 (9.1)	150	ND 21 (14)	0.60 [0.31; 1.19]; 0.144[b]
KEYNOTE 042 (data cut-off 26/02/2018)		ND		ND	ND
Indirect comparison using common comparators[c]:					
atezolizumab vs. pembrolizumab					0.20 [0.06; 0.63]; 0.007[d]

Table 1: Results (side effects) – RCT, indirect comparison: atezolizumab vs. pembrolizumab, patients with high PD-L1 expression (multipage table)

Outcome category Outcome	Atezolizumab or pembrolizumab		Platinum-based chemotherapy		Group difference
Comparison Study	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
a. HR and 95% CI: unstratified analysis, p-value from log-rank test. b. HR and 95% CI: Cox regression model, stratified by geographical region, ECOG PS and histology; p-value from Wald test. c. Indirect comparison according to Bucher [7]. d. IQWiG calculations from effect estimator. e. Operationalized as CTCAE grade ≥ 3. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus					

2.1 Summary

The adjusted indirect comparison reveals an advantage for atezolizumab in the outcome of discontinuation due to AEs.

The G-BA decides on the added benefit.

References

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